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EXAMINER	
MOSHER, MARY	

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,006	LAI ET AL.	
	Examiner	Art Unit	
	Mary E. Mosher, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24 and 26-33* is/are pending in the application.

4a) Of the above claim(s) *24,27-29 and 33* is/are withdrawn from consideration.

5)☒ Claim(s) *23* is/are allowed.

6)☒ Claim(s) *1-22,26,30 and 31* is/are rejected.

7)☒ Claim(s) *32* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/10/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of group I, species 5H2 in the reply filed on 6/9/08 is acknowledged.

Claims 24, 27-29, and 33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 6/9/06.

Claim Rejections - 35 USC § 112

Claims 1, 2, 3, 12, 13, 14-22, 26, 30, and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claims 2 and 3, "said antibody fragment" lacks antecedent.

Claims 1, 26, and 30 are drawn in part to a humanized chimpanzee monoclonal antibody that neutralizes or binds dengue virus. If the antibody is fully humanized, how can one determine that the CDRs were derived from a chimpanzee? If there are no disclosed characteristics that permit recognition of chimpanzee origin, the metes and bounds of the claimed antibodies are unclear. This affects dependent claims 2, 3, 14-22, 31.

Claims 12 and 13 are confusing in reciting "the CDR amino acid sequences of SEQ ID NO:1" (or "...of SEQ ID NO:9"). It is not clear whether or not the claims require the recited sequence, like claim 7, or if the claims require only the CDR sequences (SEQ Ids 3, 5, 7; 11, 13, 15 respectively).

Claims 4-12, 14-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are drawn to a genus, the genus of antibodies that bind the same antigen as antibody 5H2, and comprise a CDR3 region comprising SEQ ID NO:7, which is only 17 amino acids long. The specification teaches reduction to practice of one species of molecule within that genus, an antibody with CDRs of SEQ Ids 3, 5, 7, 11, 13, and 15. It is well established in the art that the formation of an intact antigen-binding site of all antibodies requires the association of the complete heavy and light chain variable regions of a given antibody, each of which comprises three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, (textbook), 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to

column 2, line 9 and lines 27-30). It is unlikely that molecules which contain less than the full complement of CDRs from the heavy and light chain variable regions have the required dengue binding activity. Applicants have provided insufficient guidance to the artisan to permit one to predict the range of structures involved in the other 5 CDRS in order to confer rabies neutralizing activity. Considering the broad scope of the genus, the limited teachings correlating structure with the required biological activity/function, and the single species reduced to practice, it is concluded that the specification does not reasonably convey possession of the genus of binding molecules claimed. This rejection applies to claims which specify less than all 6 of the CDRs of antibody 5H2; it is not applied to claim 13, which requires the full complement of heavy and light chain CDRs from antibody 5H2 (which are embedded within SEQ ID NOs 1 and 9).

The deposit of essential biological material plasmid PTA-5662 is noted, see specification page 10.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 17-20, 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Pupo-Antunez et al (Hybridoma 20:35-42, 2001). Claim 1 is drawn to a monoclonal antibody that binds to an antigen to which monoclonal antibody 5H2 binds. The specification indicates on page 11 that antibody 5H2 binds to the E protein of Dengue

type 4. Pupo-Antunez teaches a monoclonal antibody that binds to the E protein of Dengue type 4. The intact monoclonal antibody comprises Fd and Fab fragments. The antibody was shown to prevent disease in mice, and was able to detect virus. Therefore the reference antibody meets each and every limitation of these claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pupo-Antunez et al (Hybridoma 20:35-42, 2001) in view of Gavilondo et al (BioTechniques 29:128-145, 2000). As discussed above, Pupo-Antunez teaches a murine monoclonal antibody which was shown to prevent Dengue type 4 disease in mice. This differs from these claims, which are drawn to a nucleic acid encoding the

antibody. However, Gavilondo teaches cloning of murine antibody genes for the purpose of humanizing the antibodies, to avoid complications for use in humans. It would have been within the ordinary skill of the art to prepare a recombinant humanized version of the antibody of Pupo-Antunez, for the purpose of prophylactic and therapeutic use against Dengue 4 in humans, with reasonable expectation of success. The invention as a whole is therefore prima facie obvious, absent unexpected results.

Claims 26, 30, 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schofield et al (US 7282205) in view of Scherer et al (American Journal of Tropical Medicine and Hygiene 27:590-599, 1978, abstract only cited), with evidence by Sanna et al (Immunotechnology 4:185-188, 1999). Schofield teaches recombinant chimpanzee monoclonal antibodies directed against hepatitis A virus. Schofield teaches that chimps are susceptible to infection with hepatitis A virus and can produce antibodies that neutralize the virus, see example 1 at column 23. Schofield teaches use of bone marrow from an experimentally infected chimpanzee to make an antibody phage library, see example 1 at columns 23 and 24. Schofield explicitly discusses humanized chimpanzee antibodies, see for example column 2, lines 5-11. Schofield also teaches recloning the genes selected from the phage library into pFab-CMV to make a whole IgG molecule, see example 9 and column 30. This results in an antibody with a chimpanzee variable region and a human constant region, because pFab-CMV uses a human constant region (see Sanna as evidence). Therefore, Schofield differs from the claimed invention only in that the antibodies are directed against hepatitis A virus rather than Dengue virus type 4. However, Scherer teaches experimental infection of

chimpanzees with dengue viruses, including type 4, and teaches that the chimps make neutralizing antibodies. This is similar to the chimps of Schofield, that were experimentally infected and made neutralizing antibodies. It would have been within the ordinary skill of the art to make anti-dengue monoclonal antibodies according to the teachings of Schofield from dengue-infected chimps, similar to those taught by Scherer, to obtain anti-dengue monoclonal antibodies with the same useful properties as the anti-hepatitis A virus monoclonal antibodies of Schofield. Therefore, absent unexpected results, the invention as a whole is prima facie obvious.

Allowable Subject Matter

SEQ ID NO:7 is not taught or suggested in the prior art. Claims drawn to substantially pure antibodies with all six CDRs of SEQ ID NOs. 3, 5, 7, 11, 13, and 15, would be allowable.

Claim 32 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 23 is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary E. Mosher, Ph.D. whose telephone number is 571-272-0906. The examiner can normally be reached on varying dates and times; please leave a message.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mary E Mosher, Ph.D./
Primary Examiner, Art Unit 1648

9/11/08